16. (Twice Amended) The ligand-bonded complex according to claim 1, which comprises a dissociation constant between the target and one ligand of 1 E-8 M or greater.

17. (Twice Amended) The ligand-bonded complex according to claim 1, which comprises a dissociation constant between the target and one ligand of 1 E-7 M or greater.

REMARKS

Applicants thank Examiners Le and Counts for the courtesy of the personal interview of September 17, 2002. Reconsideration and withdrawal of the rejections of record are respectfully requested.

Interview Summary

At the September 17, 2002, interview, the Examiners in charge of the case and Applicants' representative discussed the claims, the indefiniteness rejection, and the art rejection.

Applicants' representative presented two proposed claims, which the Examiners agreed appeared to be definite. Amended claims 1 and 2 are essentially the same as the proposed claims that were discussed. Other of the claims were discussed, and it was acknowledged that an explanation of the claimed dissociation constant and the term "active principle" should be sufficient to further clarify the affected claims.

Regarding the applied art of BENZ in view of WANDS, Applicants' representative argued that there is no motivation in the applied art to combine the applied documents. Moreover, it was argued that WANDS, which is directed to detecting a "free" protein subunit, does not disclose or suggest, *inter alia*, a ligand-bonded complex comprising a ligand having an affinity for a target substance, wherein the affinity allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. These distinctions appeared to be recognized by the Examiners.

Once again, Applicants thank the Examiners for extending the courtesy of the interview. In view of the interview and the following remarks, reconsideration and withdrawal of the rejections of record are respectfully requested.

Foreign Priority

Applicants thank the Examiner for indicating in the Office Action acknowledgment of receipt of all required certified copies of priority documents from the International Bureau. Thus, Applicants claim of foreign priority is complete.

Information Disclosure Statement

Applicants thank the Examiner for indicating in the Office Action consideration of the Information Disclosure Statements filed January 30, 2002; March 19, 2002; and April 5, 2002 by initialing, signing, and returning the submitted Forms PTO-1449. Thus, the record reflects

consideration of the cited documents by the Examiner.

Status of the Claims

Claims 1-18 were originally and are now pending in the application. Claims 1-18 stand rejected under 35 U.S.C. § 112, ¶ 2, and under 35 U.S.C. § 103(a). By the present Amendment, claims 1-3, 6, 11, and 15-17 are amended.

Response to Indefiniteness Rejection

Claims 1-18 stand rejected under 35 U.S.C. § 112, ¶ 2, as allegedly being indefinite. Applicants respectfully traverse the rejection and/or submit that the rejection is moot, as set forth below.

In claim 1, the terms "sufficient," "substantially," and "even" are said to be indefinite. These words have been deleted from claim 1, and thus the rejection is believed to be moot.

In claim 2, the term "of a same kind" is said to be indefinite. The objected-to term has been deleted from claim 3, and thus the rejection is believed to be moot.

In claim 11, "active principle of a medicament" is said to be indefinite. Applicants respectfully traverse the rejection on the grounds that the meaning of the term is clear and distinct to one of skill in the art. "Active principle of a medicament" simply means a drug or active agent

in the complex. See, for example, page 8 of the specification wherein many examples are provided. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

In claim 15, the typographical error in the original claim has been corrected.

In claims, 16 and 17, the recitation of dissociation constant values is said to be indefinite. Applicants respectfully submit that one skilled in the art understands that "E-X" in this context refers to the recited power of 10, *i.e.*, $1x10^{-x}$ Thus, claim 16, for example, recites a dissociation constant of at least $1x10^{-8}$ Molar. Furthermore, Example 1 (page 11 of the specification) describes actually measuring a dissociation constant (found to be 1E-7 molar in the example) using a flow cytometer. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Applicants note that the amendment to the claims is a clarifying amendment that is cosmetic in nature and not intended to narrow the scope of the claims. Accordingly, this Amendment should not be considered a decision to narrow the claims nor as surrendering equivalents of the territory between the claims prior to the present Amendment and the amended claims. No estoppel should be attached thereto.

For at least the foregoing reasons, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, ¶ 2, are respectfully requested.

Response to Art Rejection

Claims 1-18 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,214,388 to Benz et al. ("BENZ") in view of U.S. Patent No. 4,933,275 to Wands et al. ("WANDS"). Applicants respectfully traverse the rejection.

The rejection states that BENZ discloses liposomes which comprise a target moiety (ligand) which can be antibodies, which specifically binds a target, can be directly conjugated to the liposome, and can have polyethylene glycol bonded to the targeting moiety. The rejection further states that BENZ discloses therapeutic agents entrapped in the liposome, and can comprise pharmaceutical compositions.

However, as discussed at the interview, it is acknowledged that BENZ does not disclose or suggest, *inter alia*, a ligand that specifically binds to a non-free target even in the presence of both a free target and a non-free target. Thus, an important feature of the claimed invention is not disclosed or suggested in BENZ, and one skilled in the art would not have been motivated by the applied art to modify BENZ to remedy at least this important shortcoming of BENZ.

The rejection states that WANDS discloses ligands (antibodies) that are specific for epitopes of a non-free target even in the presence of a free target and alleges that it would have been obvious to one skilled in the art to incorporate the ligands of WANDS with the complex of BENZ. With respect to claims 16 and 17, the rejection states that the claimed dissociation constants are inherent

in the combination of BENZ and WANDS.

Applicants' claim 1 recites a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least one ligand having a specific affinity for a free-target substance in the presence of both a non-free target and a free target. In this connection, *see, e.g.*, page 5 of the specification, in which the terms "non-free target" and "free target" are discussed. The specification also describes methods of determining and controlling the relative affinity of the ligand(s) for a free and non-free target. *See, e.g.*, page 5.

With this backdrop, Applicants respectfully submit that there is no motivation in the applied art to combine the documents as set forth in the rejection or modify BENZ according to WANDS, and even if combined as proposed in the rejection, the applied art does not disclose or suggest every element of the claimed invention. Specifically, BENZ does not disclose or suggest a critical feature of the invention, *i.e.*, the claimed specificity. WANDS discloses a method of detecting a "free" peptide subunit as part of a quaternary protein structure. Distinguishing between an intact native protein and a free subunit is disclosed. In essence, then, WANDS discloses an antibody that recognizes a part (i.e., a subunit) of the structure of the tetramer protein rather than the whole structure. In contrast, according to the present invention, for example, an antibody recognizes the *overall structure* of a target (non-free target) to the substantial exclusion of partial structure (free target). Thus, it appears that WANDS is directed to a fundamentally different composition, and even that the term "free" is used with a different meaning than in the present claims. Furthermore, as

noted above, a feature of WANDS is to recognize an epitope that is specific to a subunit, whereas the claimed invention makes use of differences in affinity of a ligand to free and non-free targets rather than a specific epitope. In view of the above, Applicants respectfully submit that the rejection merely recites alleged benefits of WANDS, but respectfully does not set forth a proper motivation to modify BENZ in view of WANDS, which in any case does not suggest the features not suggested in BENZ.

For at least these reasons, reconsideration and withdrawal of the rejection are respectfully requested.

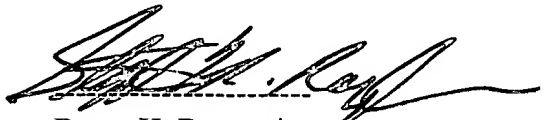
With regard to the issue of the doctrine of inherent anticipation, Applicants note that inherent disclosure can only be found in situations where the undisclosed subject matter is *necessarily* present in the disclosure. Not even probability or obviousness can satisfy this doctrine. *See, e.g.*, Trintec Indus, Inc. v. TOP-U.S.A. Corp., No. 01-1568 (Fed. Cir. July 2, 2002).

Conclusion

In view of the above, Applicants respectfully submits that all of the pending claims are allowable in their present form, and that the application is otherwise in condition for allowance. The Examiner is respectfully requested to withdraw the rejections and, as the next official action, to provide a Notice of Allowance.

If any issues remain which can be resolved by a telephone conference, or should the Examiner have any questions or comments regarding this matter, the Examiner is respectfully invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,
Toshiaki TAGAWA et al.



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P21462.A06

APPENDIX

Marked-Up Copy of Amended Claims

- - - 1. (Amended) A ligand-bonded complex comprising a microparticle [in which a microparticle is] directly or indirectly bonded to [a ligand having] at least one ligand, the ligand having an affinity for a target substance, wherein the affinity allows [of the ligand is sufficient to allow substantially] specific binding of the [ligand-bonded] complex to a non-free target [even] in the presence of both a non-free target and a free target.

2. (Amended) The ligand-bonded complex according to claim 1, wherein two or more [molecules of a single kind of the ligand] said ligands each having [substantially] the same affinity are bonded to [one] the microparticle.

3. (Amended) The ligand-bonded complex according to claim 2, wherein the complex comprises sufficient ligand [an amount of the ligand is sufficient] for reaction with the non-free target.

6. (Twice Amended) The ligand-bonded complex according to claim 1, wherein at least one [a part of or all] of the ligand molecules is [are] indirectly bonded to the microparticle by [means of] a water-soluble macromolecule.

11. (Amended) The ligand-bonded complex according to claim 10, wherein the liposome

encapsulates an active [principle] principal of a medicament.

15. (Amended) The ligand-bonded complex according to claim 14, wherein the antibody is bonded by a water-soluble [means of a wafer-soluble] macromolecule to a liposome encapsulating an anti-tumor agent.

16. (Twice Amended) The ligand-bonded complex according to claim 1, [wherein] which comprises a dissociation constant between the target and one ligand of 1 E-8 M or greater [is E-8 M or more].

17. (Twice Amended) The ligand-bonded complex according to claim 1, [wherein] which comprises a dissociation constant between the target and one ligand of 1 E-7 M or greater [is E-7 M or more]. - - -